

Importance of Sexual Transmission of Hepatitis C Virus in Seropositive Pregnant Women: A Case-Control Study

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The mode of hepatitis C virus (HCV) transmission in patients who deny parenteral exposure is still not understood. Seroprevalence studies of anti-HCV in sexually promiscuous populations and in spouses of infected patients have given contradictory results. We investigated the role of sexual transmission of HCV in a case-control study of risk factors for infection in a series of 43 anti-HCV positive pregnant women and 172 matched controls (4 for each case). In the univariate analysis, the following factors were associated significantly with anti-HCV seropositivity: low social class, unmarried, history of abortion, wounds which were sutured, tattoos, sharing toiletries with the partner, sexual contact outside the partnership without condom use, blood transfusion, and intravenous drug abuse, but only the last 3 factors remained significantly associated with HCV infection in multiple logistic regression analysis. The relative risk of HCV infection increased according to the increased number of sexual partners. Thus sexual transmission must be considered a possible mode of infection in HCV infected persons without parenteral exposures. *J. Med. Virol.* 52:164–167, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: hepatitis C transmission; epidemiology of hepatitis C

INTRODUCTION

The epidemiology of hepatitis C virus (HCV) infection is partly unknown. Parenterally transmitted infections related to transfusion of unscreened blood or to contaminated syringes and needles account for only 50% of cases with acute non-A, non-B hepatitis, acute hepatitis C, and chronic hepatitis C [Alter et al., 1990; Sherlock, 1994]. Inapparent parenteral inoculations

and sexual contacts with an infected person might explain the 50% of cases unrelated to blood transfusions and to drug misuse. Previous studies on the relative importance of sexual and household transmission of HCV and the role of medical procedures in transmission of infection gave equivocal results [Everhart et al., 1990; Eyster et al., 1991; Brackman et al., 1993; Lissen et al., 1993; Oshita et al., 1993; Osmond et al., 1993a; Osmond et al., 1993b; Wu et al., 1993; Chang et al., 1994; Thomas et al., 1994]. A better knowledge of the modes of HCV transmission is needed for the adoption of preventive measures by those at risk.

The aim of the study was to identify with a case-control study the risk factors for hepatitis C virus infection in asymptomatic pregnant women with anti-HCV using a third-generation ELISA and confirmed by RIBA.

SUBJECTS AND METHODS

Subjects

Cases and controls were recruited from a prospective study on the prevalence of hepatitis C virus infection in the general population, conducted in a large sample of pregnant women during the months of May and June 1992 in Catalonia, Spain.

Forty-three pregnant women who were found positive for anti-HCV by a third-generation ELISA (ELISA 3, Ortho Diagnostics, Raritan, NJ) and had a positive recombinant immunoblot assay (RIBA) result were included in the study. One hundred seventy-two controls were selected among women without anti-HCV, using age (± 2 years), at the same hospital for delivery as matching criteria.

HCV infection was later confirmed in anti-HCV posi-

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TABLE I. Distribution of Cases and Controls: Age, Habitat, and Place of Birth

Variable	Cases (n = 43)	Controls (n = 172)
Age (years, mean \pm SD)	28.5 \pm 4	28.5 \pm 5
Habitat		
urban ^a	77	80
rural ^a	23	20
Place of birth		
Catalonia ^a	70	67
All others ^a	30	33

^aIn percent.

tive cases by detection of HCV-RNA in serum by a nested polymerase chain reaction.

The 43 anti-HCV positive eligible cases represent 0.9% of a sample of 4,551 Spanish-born pregnant women investigated. They were selected by randomized sampling in 27 of the 34 hospitals of Catalonia with an obstetrics department, according to the yearly number of deliveries in each hospital. A sample of serum from these women was examined for anti-HCV during the 2 months of study.

The mean age, place of birth, and place of residence were similar in cases with and without anti-HCV. (Table 1).

The size of the sample was calculated according to an expected prevalence of anti-HCV of 2%, a 4% precision, and an alpha value of 0.05.

Cases and controls were interviewed at their home by the same nurse epidemiologist using a structured questionnaire concerned with potential risk factors of hepatitis C (Table II). None was aware of the results of anti-HCV testing.

Statistical Analysis

The MacNemar's test for paired data was used to analyse the association between potential risk factors for HCV infection and anti-HCV seropositivity. A *P* value of 0.05 or less was considered statistically significant. Crude odds ratio (OR) and its 95% confidence interval were calculated for each significant parameter [Schesselmann and Stolley, 1982]. Adjusted OR for each of the risk factors associated significantly with HCV infection in the univariate analysis were calculated using a multiple logistic regression analysis, using the EGRET software package (Statistics and Epidemiological Research Corporation, Seattle, WA).

RESULTS

Of the 43 anti-HCV positive cases, a well recognized parenteral risk factor for HCV infection was found in 21 (49%), blood transfusion in 7 (17%) and misuse of intravenous drugs in 14 (32%). The remaining cases had no identifiable known risk factors for hepatitis C infection.

In the univariate analysis (Table II) it was observed that in addition to the history of blood transfusion and of intravenous drug abuse, anti-HCV seropositivity was associated significantly with a low social class

(O.R.: 2.52), a patient's unmarried status (O.R.: 3.45), a history of abortion (O.R.: 2.33), presence of wounds which required suture (O.R.: 2.00), tattoos (O.R.: 15.0), unprotected sexual contact outside the partnership (O.R.: 4.79), and sharing toiletries with the partner (O.R.: 2.36). The risk of HCV infection increased with the number of sexual partners and was 14 times higher in those with more than 4 partners (O.R.: 14.7) and 3 times higher in those with 2 or 3 partners (O.R.: 3, 4) in comparison with those who had only 1 sexual partner (Table III). Multivariate analysis showed that only unsafe sexual contacts with more than one partner remained as an independent risk factor (O.R.: 2.90, 95% C.I.: 1.13–7.41), together with a history of blood transfusion (O.R.: 8.12, 95% C.I.: 1.92–34.35) and intravenous drug abuse (O.R.: 26.45, 95% C.I.: 3.26–221.1). Other potential risk factors revealed by the univariate analysis lost statistical significance by multivariate analysis (Table IV).

DISCUSSION

The results of the present study confirm that nearly 50% of patients with HCV infection have likely been infected by blood transfusion or intravenous drug abuse and that the mode of transmission is not apparent for the remaining 50%. A role for parenteral mechanisms related to medical practices, such as acupuncture, dental extractions, and surgical and nonsurgical hospitalization could not be demonstrated in the study. Tattooing, which was associated with HCV infection by the univariate analysis, lost its significance as a risk factor by multivariate analysis, owing to its association with drug use.

Chiaramonte et al. [1996] have shown that previous use of glass syringes, a history of tuberculosis, and prolonged hospitalization before 1970 were risk factors associated independently with HCV infection, particularly in middle-aged to old subjects. These factors may have played a negligible role mostly in young females, who were unlikely to have been exposed to nonsterile medical material.

The study shows an association between extramarital sexual activity and HCV seropositivity. Any woman with a history of 2–4 partners other than her regular partnership had a 2.8-fold risk of HCV infection than did any woman without extramarital sexual activity, and in those with more than 4 sexual partners the risk was more than 8-fold.

Studies addressed to assess sexual transmission of HCV infection have given contrasting results. Alter et al. [1989] found that 12% of patients with sporadic non-A, non-B hepatitis had a history of exposure to multiple heterosexual partners in the previous 6 months, but only 1% of controls without hepatitis. High anti-HCV seroprevalence rates have been found in non-drug-using heterosexual population attending STD clinics and in non-drug-using female prostitutes [Alter, 1995]. Conversely, many other studies addressed to compare the prevalence of anti-HCV in sexually promiscuous homosexual males [Osmond et al., 1983b; Domínguez

TABLE II. Risk Factors of Hepatitis C Virus Infection Among Cases and Controls and Odds Ratios (OR) Estimated by Univariate Analysis

Risk factors	Cases n°(%)	Controls n°(%)	OR	P value	CI* 95%
Parenteral					
Blood transfusion	7 (17)	9 (5)	3.15	0.009	1.35–8.01
Injection-drug use	14 (32)	4 (2)	27.00	<0.001	5.85–315.51
Tattoo(s)	4 (9)	2 (1)	15.00	<0.001	1.78–31.20
Abortion(s)	15 (35)	32 (19)	2.33	<0.001	1.32–4.17
Sutured wound(s)	18 (42)	48 (28)	2.00	0.008	1.15–3.52
Sharing toiletries	35 (81)	144 (84)	0.82	ns	0.43–1.53
Medical injection(s)	8 (19)	31 (18)	1.04	ns	0.56–1.93
Acupuncture	4 (9)	14 (8)	1.15	ns	0.48–2.77
Immunoglobulin injection(s)	8 (19)	18 (10)	1.87	ns	0.94–3.79
Health care profession	3 (7)	10 (6)	1.20	ns	0.41–3.29
Hospitalization	17 (39)	45 (26)	1.61	ns	0.95–2.73
Surgery	21 (49)	83 (48)	1.03	ns	0.62–1.68
Visits to podologist	8 (19)	19 (11)	1.61	ns	0.83–3.17
Dental procedures	29 (67)	120 (70)	0.79	ns	0.47–1.34
Sexual					
History of viral hepatitis in the sexual partner	9 (21)	17 (10)	2.07	0.032	1.01–4.38
More than 1 sexual partner and not use of condom	20 (46)	27 (16)	4.79	<0.001	2.53–9.39
2–4 sexual partners	13 (30)	24 (14)	3.41	0.003	1.41–8.22
≥5 sexual partners	7 (16)	3 (2)	14.71	<0.001	3.10–78.36
Other					
Low socioeconomic status	31 (70)	92 (53)	2.52	<0.001	1.44–4.85
Unmarried	11 (26)	12 (7)	3.45	<0.001	1.62–7.71
Sharing toiletries with a sexual partner with history of viral hepatitis	7 (16)	13 (10)	2.36	0.021	1.06–5.49

*CI = confidence interval.

TABLE III. Adjusted Odds Ratios (OR) for the Sexual Risk Factor of Hepatitis C Infection

No. of sexual partners	Cases n = 43 No.(%)	Controls n = 172 No.(%)	OR (CI) ^a	OR _{adj} (CI)
1	23 (54)	145 (84)	1.00	1.00
2–4	13 (30)	24 (14)	3.41 (1.41–8.22) ^c	2.81 (1.14–6.89) ^d
>4	7 (16)	3 (2)	14.71 (3.10–78.36) ^b	8.69 (1.32–57.19) ^c

^aOR adjusted for injection-drug use, transfusion, social class, and marital status by multiple logistic regression analysis.^bP < 0.001.^cP < 0.005.^dP < 0.05.

et al., 1994], heterosexual persons attending STD clinics [Thomas et al., 1994], prostitutes [Lissen et al., 1993; Wu et al., 1993], and sexual partners of patients with chronic hepatitis C [Everhart et al., 1990; Brackman et al., 1993; Oshita et al., 1993; Osmond et al., 1993a; Akahame et al., 1994] with that of blood donors of the same area either failed to demonstrate sexual transmission of hepatitis C or suggested that such transmission occurred at a very low level of efficiency, much lower than that of hepatitis B virus or human immunodeficiency virus. Several sources of bias in the latter studies, such as the use of a first-generation ELISA, which had a low sensitivity and specificity, and the inappropriate use of blood donors as a control group, were avoided in the present study.

TABLE IV. Risk Factors Associated With HCV Infection. Adjusted Odds Ratios Derived From Multiple Regression Analysis

Risk factors	OR _{adj}	95% CI	P value
Blood transfusion	8.12	1.92–34.35	0.004
I.V. drug use	26.46	3.26–221.10	0.002
More than 1 sexual partner and no use of condom	2.90	1.13–7.41	0.026
Tattoos	18.15	0.45–759.10	ns
Low socioeconomic status	2.01	0.75–5.40	ns
Sutured wounds	1.80	0.75–4.29	ns
Sharing toiletries with a sexual partner with history of viral hepatitis	1.69	0.38–7.45	ns
Abortions	1.10	0.37–3.29	ns
Unmarried	1.61	0.30–8.64	ns

In conclusion, the findings suggest that sexual transmission may play a role for HCV transmission in an undetermined proportion of infected persons without apparent parenteral exposure. Although the efficiency of this route of transmission may be low, the relatively high rate of persistent HCV infection in the adult general population as the reservoir of potentially infected persons and the high frequency of sexual contacts provide multiple opportunities for transmission of HCV.

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